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## Facsimile Cover Sheet

**TODAY'S DATE:** November 22, 2005

**PLEASE DELIVER THE FOLLOWING MATERIALS TO:**

Examiners Name: Richard G. Hutson  
Central fax number: (571) 273-8300  
Group number: 1652

**THIS MESSAGE IS FROM:**

Name: Sheldon O. Heber  
Phone No.: (732) 594-1958 Fax No: (732) 594-4720  
Mail Location: RY 60-30

**RE:** U.S. Appl. Serial No.: 10/085,476  
Filing Date: February 27, 2002  
Applicants File Ref: ITR0002PCA  
For: METHOD FOR REPRODUCING IN VITRO THE RNA-  
DEPENDENT RNA POLYMERASE AND TERMINAL  
NUCLEOTIDYL TRANSFERASE ACTIVITIES  
ENCODED BY HEPATITIS C VIRUS (HCV)

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NOV 22 2005

PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: De Francesco, R. *et al.*

Serial No.: 10/085,476

Case No.: ITR0002PCA

Art Unit: 1652

Filed: February 27, 2002

For:

METHOD FOR REPRODUCING IN VITRO  
THE RNA-DEPENDENT RNA  
POLYMERASE AND TERMINAL  
NUCLEOTIDYL TRANSFERASE  
ACTIVITIES ENCODED BY HEPATITIS C  
VIRUS (HCV)

Examiner: Huston, Richard G

Commissioner for Patents  
P.O. Box 1450  
Alexandria VA 22313-1450COMMUNICATION AFTER FINAL REJECTION

Sir:

Enclosed is a Notice of Appeal along with a copy of the following previously mailed documents (mailed November 21, 2005): (1) a Pre-Appeal Brief Request for Review; (2) Arguments Accompanying Request for Review; and (3) Petition for Extension of Time under § 1.136(a). The Notice of Appeal, which is mentioned in the Pre-Appeal Brief Request for Review, was advertently omitted from the November 21, 2005 mailing.

The present communication is being faxed to provide a complete response that includes a Notice of Appeal. On November 22, 2005 applicants realized a Notice of Appeal was not included with the previously mailed documents, and contacted the examiner to inform him of the mistake and that a complete response is being sent by facsimile. Applicants apologize for any confusion.

## 37 C.F.R. 1.8 Certificate of Transmission

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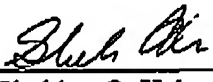
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Jodi Hobbs

Serial No.: 10/085,476  
Case No.: ITR0002PCA

Accordingly the claims are in condition for allowance. Please charge deposit account 13-2755 for fees due in connection with this communication. If any time extensions are needed for the timely filing of the present communication, applicants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

By   
Sheldon O. Heber  
Reg. No. 38,179  
Attorney for Applicant(s)

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PTO/SB/33 (07-05)

Approved for use through xx/xx/200x. OMB 0851-0001

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<b>PRE-APPEAL BRIEF REQUEST FOR REVIEW</b>		Docket Number (Optional) <b>ITR0002PCA</b>	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on <u>11-21-05</u> Signature <u>Sheldon O. Heber</u> Typed or printed name <u>Sheldon O. Heber</u>		Application Number <b>10/085,476</b>	Filed <b>02/27/2002</b>
		First Named Inventor <b>De Francesco, Raffaele et al.</b>	
		Art Unit <b>1652</b>	Examiner <b>Hutson, Richard G.</b>
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.  This request is being filed with a notice of appeal.  The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided.			
I am the <input type="checkbox"/> applicant/inventor. <input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/95) <input checked="" type="checkbox"/> attorney or agent of record. Registration number <u>38,179</u> <input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____		<u>Sheldon O. Heber</u> Signature <u>Sheldon O. Heber</u> Typed or printed name <u>(732) 594-1928</u> Telephone number <u>11-21-05</u> Date	
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.			
<input type="checkbox"/> *Total of _____ forms are submitted.			

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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NOV 22 2005

PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: De Francesco, R. *et al.*

Serial No.: 10/085,476

Case No.: ITR0002PCA

Art Unit: 1652

Filed: February 27, 2002

Examiner: Huston, Richard G

For: METHOD FOR REPRODUCING IN VITRO  
THE RNA-DEPENDENT RNA  
POLYMERASE AND TERMINAL  
NUCLEOTIDYL TRANSFERASE  
ACTIVITIES ENCODED BY HEPATITIS C  
VIRUS (HCV)Commissioner for Patents  
P.O. Box 1450  
Alexandria VA 22313-1450Arguments Accompanying Request for Review

Sir:

Applicants request reconsideration of the final rejection of claims 12, 14, 17, 18, 22, and 23, maintained in the Advisory Action mailed 10/28/05. The advisory action also indicated that claims 20 and 21 are allowed.

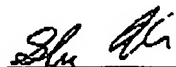
Claims 12, 14, 17, 18, 22, and 23 are directed to a method for identifying a HCV RNA-dependent RNA polymerase inhibitor involving the *in vitro* use of a composition comprising HCV NS5B recombinant protein expressed by either a eukaryotic or prokaryotic heterologous system. Claims 12, 14 and 17 also include a description indicating the NS5B protein is purified to apparent homogeneity.

## 37 C.F.R. 1.8 Certificate of Mailing

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MERCK &amp; CO., INC.

By



Date November 21, 2005

Sheldon O. Heber

Serial No.: 10/085,476  
Case No.: ITR0002PCA

Claims 12, 14, 17, 18, and 22-23 stand rejected as allegedly obvious based on Tomei et al. (Journal of Virology 67(7):4017-4026, July 1993). The rejection is based on Tomei et al. indicating that the HCV NS5 region is cleaved into products of 47 kDa (NS5A) and 65 kDa (NS5B); and Tomei et al. suggesting, based on a GDD sequence, that NS5B may act as a viral replicase. (For example, see the Final Rejection mailed 7/27/05, at page 3 and Advisory Action Mailed 10/28/05 at page 2, 6<sup>th</sup> paragraph.)

It is respectfully submitted that the final rejection of claims 12, 14, 17, 18, 22, and 23:

- (I) Improperly fails to consider the prior art as a whole in evaluating the expectation of success; and
- (II) Improperly fails to consider arguments concerning apparent failure and difficulty encountered by others.

The prior art speculations concerning a possible role for NS5B and the prior art uncertainty as to whether NS5B is an authentic HCV protein, taken together, do not provide: (1) a motivation to modify Tomei et al. to obtain the claimed assay; or (2) a reasonable expectation of success in modifying Tomei et al. to obtain the claimed assay. In addition, secondary considerations also point out the non-obviousness of the claimed invention.

**I. The Prior Art as a Whole Fails to Provide a Reasonable Expectation of Success in Using NS5B for Providing RNA-Dependent RNA Polymerase Activity in an Assay to Screen for Inhibitors**

The outstanding rejection fails to consider the prior art uncertainties as to whether NS5B is an expression artifact. Instead, the examiner takes the position that applicants have not provided evidence that the Tomei et al. speculations are in fact incorrect. (For example, see the Final Rejection mailed 7/27/05, at page 6, 3<sup>rd</sup> paragraph, and Advisory Action Mailed 10/28/2005 at page 2, 6<sup>th</sup> paragraph.)

The rejection improperly fails to consider other statement in the prior art contradicting Tomei et al. Prior art uncertainty concerning the relevance of recombinantly produced NS5B to authentic HCV proteins is: (1) reflected in differences between published results obtained from HCV infected liver cell versus recombinantly processed HCV polyprotein; and (2) are also noted

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Case No.: ITR0002PCA

in cautionary language used in publications concerning recombinant NS5B. (For example, see applicant's Amendment mailed 9/14/05 on pages 5-6, under the heading "Uncertainty Concerning Authentic HCV Proteins".)

Applicants are not arguing that the skilled artisan as of today would expect NS5B to be an expression artifact and not provide activity. In hindsight, as demonstrated by the present application, it is known that NS5B provides for RNA-dependent RNA polymerase activity. That the inventors were ultimately successful is irrelevant to whether the skilled artisan would have reasonably expected success at the time the invention was made. *Life Technologies Inc. v. Clontech Laboratories Inc.*, 56 USPQ2d 1186, 1192 (Fed. Cir. 2000).

As noted by the Manual of Patent Examining Procedure (MPEP):

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. (Citations omitted, emphasis added.)

(MPEP Rev. 3, August 2005, Section 2141.3 at p. 2100-132, 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph.)

The rejection fails to weigh the conflicting prior art statements. In weigh the conflicting statements, the cautionary language provided in Tomei et al. itself needs to be considered. (For example, see applicant's Amendment mailed 9/15/05 on page 6, 2<sup>nd</sup> paragraph.) It is respectfully submitted that proper weighing of such statements indicates a reasonable expectation of success is lacking.

## II. Secondary Considerations Further Support the Non-Obviousness of the Pending Claims

Additional considerations illustrating the inventive nature of the pending claims include:

- Apparent failure and difficulty encountered by others in successfully purifying HCV RNA-dependent RNA polymerase;
- Apparent failure and difficulty encountered by others in demonstrating the HCV region responsible for RNA-dependent RNA polymerase; and
- A long-felt need for an HCV RNA-dependent RNA polymerase assay to look for polymerase inhibitors.

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(For example, see Applicant's Amendment mailed 9/15/05 on pages 6-7, under the heading "Apparent Failure, Difficulty Encountered by Others and Long-Felt Need".)

The examiner's position appears to be that the secondary considerations do not relate to the rejections. However, the examiner fails to provide any rationale as to why the noted secondary considerations are not directed to the rejections. (For example, see Final Rejection Mailed 7/27/05 at page 7, 3<sup>rd</sup> paragraph, and Advisory Action mailed 10/28/05 at page 2, 7<sup>th</sup> paragraph.)

Difficulties in successfully purifying an active HCV RNA-dependent RNA polymerase is relevant to limitations provided in claims 12, 14 and 17. These claims include a description indicating that the NS5B protein is purified to apparent homogeneity.

Apparent failure and difficulty encountered by others in demonstrating the HCV region responsible for RNA-dependent RNA polymerase is relevant for limitations provided in the all rejected claims. The rejected claims indicate using NS5B in an assay for RNA-dependent RNA polymerase inhibitors.

Long-felt need for an HCV RNA-dependent RNA polymerase assay to look for polymerase inhibitors is relevant to limitations provided in all the rejected claims. The rejected claims are directed to an assay that can be used to identify HCV RNA-dependent RNA polymerase inhibitors.



Serial No.: 10/085,476  
Case No.: ITR0002PCA

Accordingly the claims are in condition for allowance. Please charge deposit account 13-2755 for fees due in connection with this communication. If any time extensions are needed for the timely filing of the present communication, applicants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

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